to page 13 line 17. Claim 49 is supported on page 29 line 1 to 8.

It is also noted that the Examiner has objected to the specification as allegedly containing phrases that are trademarked. In response, the words or phrases "BioNick", "Photometric Cooled-CCD", "Nybond", and "RadPrime" were checked on Trademark-scan to determine if they were indeed registered. According to the search, none of these phrases or words are registered trademarks, and as such, the Applicant asserts that the Examiner's request that these phrases be denoted as registered trademarks is in error.

Therefore, upon entry of the present amendment, Claims 1 and 31-49, which are drawn to nucleic acids and fragments thereof that encode the Down Syndrome-Cell Adhesion Molecule polypeptide, are pending in the instant application.

I. The Rejection Under 35 U.S.C. § 101, Should Be Withdrawn

Claims 1-10, 12, 20 and 30, drawn to nucleic acid molecules that encode a novel Down Syndrome-Cell Adhesion Molecule (DS-CAM) and allelic variants thereof, are rejected under 35 U.S.C. § 101. The Examiner contends that the claimed invention is not supported by either a specific asserted utility or a well established utility.

Applicant emphatically disagrees and assert that the instant specification provides a disclosure which describes several specific utilities of the invention.

The present invention is directed to a previously unknown human gene that maps to a region of a human chromosome that is different in individuals with Down Syndrome relative to individuals without Down Syndrome. The claims are drawn to isolated nucleic acids comprising the nucleotide sequence of a novel mammalian DS-CAM gene and cell lines which express the claimed nucleic acids.

The specification asserts many credible utilities for the claimed isolated nucleic acids, including but not limited to

genetic testing (see page 43 line 3 to page 44 line 4) and diagnosis of Down Syndrome (see specification at page 44 line 18 to page 45 line 21). In addition, the isolated nucleic acid molecule can be used in mapping of this important region of chromosome 21 (see specification at page 56 line 29 to page 57 line 2). Thus, Applicant submits that the isolated nucleic acids encoding the DS-CAM have several important and credible utilities and are fully supported and enabled by the instant specification.

In rejecting the claimed nucleic acids, the Examiner contends that the disclosure has not established a correlation with Down Syndrome and the claimed nucleic acids of the invention and further suggests that the Applicant has failed to isolate a cDNA of a gene. The Examiner argues that the specification does not provide guidance regarding the functional role of the claimed nucleic acids in Down Syndrome or guidance that the claimed nucleic acids may be utilized to diagnose and treat Down Syndrome.

In response, the Applicant respectfully points out that in order to meet the utility requirement, a new product or process must be operable and capable of use, and achieve some minimum human purpose that is not illegal, immoral, or contrary to public policy. Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 1325, 6 U.S.P.Q.2d 1065 (D. Del. 1987), aff'd, 865 F.2d 1247, 1252, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989).

In addition, it must be capable of some beneficial use in society, and be more than just a mere curiosity; it must exhibit a specific benefit in available form. Brenner v. Manson, 383 U.S. 519 (1966). However, commercial marketability is not required. Studiengesellschaft Kohle mbH v. Eastman Kodak Co., 616 F.2d 1315, 1339, 206 U.S.P.Q. 577, 598 (5th Cir. 1980), cert. denied, 449 U.S. 1014 (1980); In re Langer, 503 F.2d 1380, 1393, 183 U.S.P.Q. 288 (C.C.P.A. 1974). Furthermore, *in vitro* tests can be sufficient to manifest a practical utility **even though they may not establish a**

specific therapeutic use. Cross v. Iizuka, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985); Nelson v. Bowler, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980).

Moreover, a patent applicant need show utility for only one disclosed purpose. Raytheon Co. v. Roper Corp., 724 F.2d 951, 958, 220 U.S.P.Q. 592 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984); Ex parte Lanham, 121 U.S.P.Q. 223 (Pat. Off. Bd. App. 1958). Further, as long as the asserted utility of the claimed invention is credible, there is no basis to challenge such a claim on the basis that it lacks utility under 35 U.S.C. § 101 (MPEP § 2107.01(c); emphasis in original). It is not necessary to provide evidence that an asserted utility is true "beyond a reasonable doubt" in order to support a claimed utility. In re Irons 340 F.2d 974, 978 (CCPA 1965). Rather, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (MPEP § 2107.01(f); emphasis in original).

Applicant also points out that with respect to proof of utility and operability of inventions, the Patent Office has long applied a rule that the invention is presumed to be operable as disclosed. The Patent Office bears the initial burden of showing that there is a reasonable doubt as to the truth of the patent applicant's assertions, upon which the burden of proving operability and utility shifts to the applicant. Fregeau v. Mossinghoff, 776 F.2d 1034, 1038, 227 U.S.P.Q. 848, 851-52 (Fed. Cir. 1985); In re Langer, 503 F.2d 1380, 183 U.S.P.Q. 288 (C.C.P.A. 1974). The standard for shifting the burden of proof to the applicant in cases such as the instant one is whether one of ordinary skill in the art to which the invention pertains would have reason to question the truth of applicant's statements regarding utility. In re Langer, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288 (C.C.P.A. 1974).

In the instant case, the Examiner has not come forward with appropriate evidence to show that one skilled in the art would doubt the utility of the nucleic acids of the present

invention and further, the Examiner has not provided any objective reason to doubt that the Applicant has in fact isolated the gene that is described and claimed in the present application. Rather, the Examiner appears to be rejecting the claims because she doubts that the claimed nucleic acids are involved in the mechanism of Down Syndrome. In view of the applicable case law, Applicant respectfully submits that such inquiry is misplaced and unnecessary.

Applicant respectfully submits that this rejection is in error, and requests its withdrawal.

II. The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

The specification is objected to and Claims 1-10, 12, 20 and 30, drawn to nucleic acid molecules that encode DS-CAM and allelic variants thereof, are rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that the instant specification as originally filed does not provide an enabling disclosure for how to use the claimed DS-CAM nucleic acid molecules, vectors and host cells. Applicant respectfully disagrees and asserts that the instant specification provides a disclosure which fully enables one of skill in the art to make and use the claimed isolated nucleic acid molecules without undue experimentation.

The test for enablement is whether one of ordinary skill in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. U.S. v. Telectronics Inc. 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988).

Applicant reiterate that the present invention is directed to a previously unknown human gene that maps to a region of a human chromosome which is frequently altered in patients with Down Syndrome. The claims are drawn to isolated nucleic acids comprising the nucleotide sequence of this novel gene, kits containing the nucleic acids, cells which express

the claimed nucleic acids and methods for expressing the protein encoded by the nucleic acids.

Applicant respectfully asserts that it is not necessary for the specification to demonstrate the causal/functional role of the DS-CAM nucleic acids in Down Syndrome in order to satisfy the "how to use" requirement of Section 112, as erroneously asserted by the Examiner. In order for the instant application to be in compliance with the utility requirements of 35 U.S.C. §101 and §112, the specification must assert a reasonable expectation of credible utility of the claimed invention, i.e., the isolated nucleic acid molecules, and provide an enabling disclosure for at least one of the asserted utilities, namely, the use of the claimed isolated nucleotide sequences for mapping human chromosome 21q.

Applicant has demonstrated that this novel gene is located in the long arm of human chromosome 21q, a region in which the chromosomal alteration known as trisomy 21 associated with Down Syndrome had previously been reported to map. Applicant contends that the scientific community and those in the art of genetic mapping of Down Syndrome recognize the potential linkage of several genetic loci on chromosome 21 with Down Syndrome, as well as the need for markers to finely map these chromosomal regions. In addition, given that this region of chromosome 21 is likely to contain many genes with plausible connections to the various manifestations of Down Syndrome, there is a need for markers to finely map this region of chromosome 21. The claimed nucleic acid molecule can be used as a marker for mapping the region of the long arm of human chromosome 21q spanned by chromosomal markers D21S55 and MX1 (e.g., see page 50, lines 13 to 16 of the instant specification).

The specification provides the claimed nucleic acid sequences, vectors and cell lines containing the nucleic acid as well as the novel proteins encoded by the claimed nucleic acids which have potentially significant pharmaceutical value.

For instance, Applicant has provided a number of utilities for the claimed nucleic acid including diagnostic evaluation, genetic testing and prognosis of a DS-CAM disorder or a neuropsychiatric disorder. Such methods may comprise simply measuring DS-CAM gene expression in a patient sample by Northern blot analysis as described in the instant specification (e.g., see pages 57-58).

The instant specification is clearly, and at the very least sufficient to support the described use and enablement of the claimed nucleic acids as chromosomal markers for mapping of the long arm of human chromosome 21q. It cannot be seriously contended that the asserted use contravenes established scientific principles and beliefs. Moreover, the Utility Examination Guidelines (the "Guidelines", 60FR 36263) which are applicable to issues of enablement under 35 U.S.C. § 112 (see Guidelines, Legal Analysis Section I.D. and n. 30, and In re Brana, 34 USPQ2d 1436), specifically state that the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt," or statistically certain. Rather, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. (Guidelines, Legal Analysis of Section II.G.).

Here, where the Applicant's data actually demonstrates that the claimed nucleic acid molecules can be used as fine mapping tools for the long arm of human chromosome 21q, for which there exists an art recognized need. Thus, the legal requirements for utility and enablement of the claimed DNAs are satisfied.

In view of the foregoing, the Applicant respectfully submits that the rejection under 35 U.S.C. § 112, first paragraph, has been overcome and should be withdrawn.

III. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 1-10, 12, 20 and 30 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

In response, the pending claims have been amended to more particularly recite nucleic acids of the invention, including nucleic acids that hybridize under highly stringent conditions to the complement of such nucleic acid molecules. These stringent hybridization conditions are disclosed on page 16, lines 23-32, of the instant specification.

In addition, the pending claims do not recite (without conceding that the phrases are indefinite) abbreviations or the phrases "degenerate DNA", "biologically active", "substantially the same", all of which the Examiner has found objectionable.

In view of the foregoing amendments and replacement claims, Applicant respectfully submits that the rejections under 35 U.S.C. §112, second paragraph, have been obviated and should be withdrawn.

IV. The Rejection Under 35 U.S.C. § 102(a), Should Be Withdrawn

Claims 1-3 are rejected under 35 U.S.C. § 102(a), second paragraph, as anticipated by Korenberg et al., 1994, Proc. Natl. Acad. Sci. 91:4997-5001 ("Korenberg"). The Examiner alleges that Korenberg teaches isolated nucleic acids from patients with Down Syndrome and that the presently claimed invention would inherently be encoded by these nucleic acids. The Examiner also alleges that the Korenberg nucleic acids would hybridize to SEQ ID NO:1 of the present invention.

The legal test for anticipation under 35 U.S.C. § 102 requires that each and every element of the claimed invention be disclosed in a prior art reference in a manner sufficient to enable one skilled in the art to reduce the invention to practice, thus placing the public in possession of the invention. W.L. Gore Associates v. Garlock, Inc., 721 F.2d

1540, 1554 (Fed. Cir. 1983) cert. denied 469 U.S. 851 (1984); In re Donohue, 766 F.2d 531 (Fed. Cir. 1985). Anticipation under 35 U.S.C. § 102 requires identity of invention. Scripps Clinic & Research Fdn. v. Genentech Inc., 927 F.2d 1565 (Fed. Cir. 1991).

The well recognized legal standard for anticipation was recently iterated by the Court of Appeals for the Federal Circuit ("CAFC") in Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565 (Fed. Cir. 1991). The CAFC made it absolutely clear that "[i]nvalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference ... [and] ... [t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person or ordinary skill in the field of the invention." Scripps v. Genentech, 927 F.2d at 1576. Absence from a cited reference of any element of a claim of a patent negates anticipation of that claim by that reference. Atlas Powder Co. v. E.I. Dupont de Nemours & Co., 224 U.S.P.Q. 409 (Fed. Cir. 1984).

In the event that a reference does not explicitly teach all the elements of a claim, anticipation can only be shown by inherency if the cited reference makes clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by one of ordinary skill in the art. Continental Can Company USA, Inc. v. Monsanto Company, 948 F.2d 1264 (Fed. Cir. 1991) (emphasis added). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. In re Oelrich, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Korenberg merely describes the mapping of the physical location of human chromosomal markers that are associated with Down Syndrome by quantitative Southern blotting and fluorescent in situ hybridization (see paragraph bridging page 4996 and 4997.) The mapping was performed using cell lines

from patients with Down Syndrome and previously defined DNA markers. While it is true that the presently claimed genomic DNA is present on the human chromosome 21 that is the subject of Korenberg's study, however, Korenberg does not teach an isolated nucleic acid that encodes a DS-CAM polypeptide as disclosed and claimed in the instant application. In fact, Korenberg fails to disclose the nucleotide sequence of any gene on human chromosome 21. In addition, Korenberg does not teach a cDNA of DS-CAM.

Accordingly, this reference does not anticipate the present invention. Applicant respectfully submits that the rejection under 35 U.S.C. § 102(a) is in error and requests that this rejection be withdrawn.

V. The Rejections Under 35 U.S.C. § 102(b), Should Be Withdrawn

Claims 1-3, 6-9 are rejected under 35 U.S.C. § 102(b) as anticipated by GenBank Accession No. F13426 or alternatively as anticipated by GenBank Accession No. Z41519. Applicant respectfully disagrees.

Applicant points out that the nucleotide sequence Z41519 is not identical to any of the claimed nucleic acids. The nucleotide sequence Z41519 is merely similar to the human DS-CAM nucleic acid in the 3' untranslated region, and thus, does not encode any amino acid sequence of DS-CAM. The nucleotide sequence F13426 is not identical to and is merely similar to a portion of the claimed nucleic acid that encodes the cytoplasmic portion of the DS-CAM protein.

As noted above, the legal standard for an anticipation rejection is as follows. "A rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference." In re Paulsen, 30 F.3d 1475, 31 USPQ2d 1671 (Fed. Cir. 1994).

Applicants respectfully submit that the amended claims do not recite any nucleic acid molecules consisting of a

nucleotide sequence that is the same as the cited nucleic acids in the database. Nor do the amended claims cover a nucleic acid comprising the nucleotide sequences that is similar to the nucleotide sequences of F13426 or Z41519 which would hybridize to the recited nucleotide sequences under the recited hybridization stringency conditions.

In view of the foregoing, Applicant respectfully submits that these rejections have been overcome and/or obviated and request that the 35 U.S.C. § 102(b) rejections be withdrawn.

VI. The Rejection Under 35 U.S.C. § 103(a), Should Be Withdrawn

Claims 1, 2, 10, 12, 20 and 30 are rejected under 35 U.S.C. § 103(a), as allegedly obvious in view of GenBank Accession No. F13426 or GenBank Accession No. Z41519 in combination with Gallatin et al., U.S. Patent No. 5,525,487 ("Gallatin").

Gallatin discloses DNA sequences encoding a novel human intercellular adhesion molecule polypeptide (designated "ICAM-R") along with methods and materials for production of the polypeptide by recombinant procedures; antibodies specific for ICAM-R; and uses thereof. The Examiner contends the claimed invention is obvious in view of the combined teachings of GenBank Accession No. F13426 or GenBank Accession No. Z41519 and Gallatin, since Gallatin teaches methods of making a polypeptide, DNA primers for amplification, radiolabeled oligonucleotides, etc.

Applicant respectfully disagrees with this rejection for the following reasons. As discussed above with respect to the response to the Examiner's Section 102 rejections, each of the sequences of GenBank, F13426 and Z41519, do not read on any of the amended or new claims. There is no teaching or suggestion whatsoever in these sequences that they may be related to a nucleotide sequence encoding a cellular adhesion molecule, such as Gallatin. Thus, there is no reason to combine these sequences with the teachings of Gallatin.

Moreover, there is no teaching or suggestion of the claimed nucleic acids of the invention in Gallatin. The principle that the prior art must contain a suggestion of the desirability of the proposed combination of isolated disclosures in order to render an invention obvious has been espoused by the United States Court of Customs and Patent Appeals in Application of Bergel, 292 F.2d 955, 130 U.S.P.Q. 206 (C.C.P.A. 1961) and was reaffirmed by the Court of Appeals for the Federal Circuit in In re Sernaker, 702 F.2d 989, 217 U.S.P.Q. 1 (Fed. Cir. 1983) and in In re Grabiak, 769 F.2d 729, 226 U.S.P.Q. 870 (Fed. Cir. 1985). Applicant submits that there is no motivation or suggestion to modify Gallatin or to combine it with the cited GenBank sequences.

Furthermore, Applicant submits that any rejection of the instant claims under § 103 would indicate the improper use of hindsight gained from Applicant's own specification. Hindsight should be avoided in applying the nonobviousness requirement. Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." In re Fine, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988).

Without the benefit of hindsight, the claimed invention could not have been foreseen by a person of ordinary skill in the art, since there was no suggestion of them in the art and their various utilities in Down Syndrome diagnosis could not have been predicted.

Thus, in view of the above-made arguments and amendments, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendments and remarks into the file of the above-captioned application. Applicant believes that each ground for rejection or objection has been successfully overcome or obviated and that the application is in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application is earnestly requested.

Respectfully submitted,

Laura A. Coruzzi By: [signature] 40,258

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